"Ossifying" mucoepidermoid carcinoma: A deceptive clinical presentation

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Mucoepidermoid carcinoma is the most common salivary gland malignancy, accounting for 27% of all salivary gland cancers. Identified in 1921 and first analyzed in 1945, mucoepidermoid carcinoma has demonstrated a widely diverse histology with several morphologic variants having been described. One rare feature is the formation of intratumoral bone, which has been previously reported once in the English language literature. Though the etiology of these calcifications is still not known, it is believed that this finding is independent of overall disease prognosis. This case report illustrates this unusual feature in a 48-year-old Hispanic woman who initially presented with a floor of mouth swelling. Computed tomography examination subsequently revealed a soft tissue mass with intralesional radiopacities. Despite its relative rarity, it is important for practitioners to be aware of this unique presentation in that it may help to avoid misdiagnosis and delays in treatment. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:217–220)

Malignancies of the salivary glands are relatively rare, accounting for only 3% of all head and neck cancers.[1,2] Mucoepidermoid carcinoma (MEC) is the most common of these, making up 27% of all salivary gland malignancies.[2,3] MEC is most commonly found in the parotid gland, followed by the minor salivary glands, where they most frequently involve the palate and buccal mucosa.[3] These neoplasms are slightly more common in women, typically in their third to sixth decades of life.[4-6]

Histologically, MEC is composed of 3 basic cell types: mucous cells, intermediate cells, and epidermoid cells.[5] This histologic profile along with other morphologic features allows for the classification of MEC into low-, intermediate-, or high-grade tumors.[4,7] The tumor grade correlates with the prognosis of the disease.[4,7] The 2 most widely used grading systems are the Armed Forced Institute of Pathology (AFIP) and Brandwein criteria.[8,9] Furthermore, several variants of MEC have been identified. The most common is conventional MEC, followed by clear cell, sclerosing, oncocytic, sebaceous, and spindle cell subtypes.[10]

Despite the histologic diversity among MEC subtypes, there is limited information regarding dystrophic calcifications and intratumoral bone formation occurring in these tumors.[10-15] The first reported case of calcifications in MEC was documented in 1987.[12] Subsequent studies reported the scarcity of these findings and associated calcifications with higher histologic grade and poorer prognosis.[13,14] Upon review of the relevant literature, only one other case of intratumoral bone formation has been reported.[15] We report a case of MEC with intratumoral bone formation and briefly reviews the literature regarding calcification and bone formation in MEC.

CASE REPORT

A 48-year-old Hispanic female patient presented to Nassau University Medical Center's Oral and Maxillofacial Surgery clinic with the complaint of left-sided floor of mouth swelling. The patient reported that the swelling had caused mild episodic pain over the course of a year, stating that the swelling had slightly increased over time. Her medical history was significant for controlled diabetes and hypothyroidism. Clinical examination revealed left floor of mouth elevation (Figure 1) that was soft but mildly tender on palpation. The overlying mucosa was normal in color and Wharton's ducts were patent with adequate salivary flow expressed bilaterally. No palpable lymphadenopathy was noted on examination. A panoramic radiograph demonstrated no obvious dentoalveolar etiology.

A clinical diagnosis of ranula was made and, after a negative aspiration, an incisional biopsy was then completed with marsupialization of the overlying mucosa. A normal-appearing glandular specimen was sent for histologic examination, which was reported as "sclerosing sialadenitis that is commonly associated with mucocele." On follow-up, the patient demonstrated normal healing of the surgical site but with persistent left-sided floor of mouth elevation. Maxillofacial computed tomography (CT) without contrast was then obtained. It demonstrated "hyperemia and mass-like enlargement of the left sublingual gland measuring approximately 2.4 × 1.4 cm with increased

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Received for publication Jun 10, 2020; returned for revision Oct 3, 2020; accepted for publication Oct 11, 2020.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2020.10.011

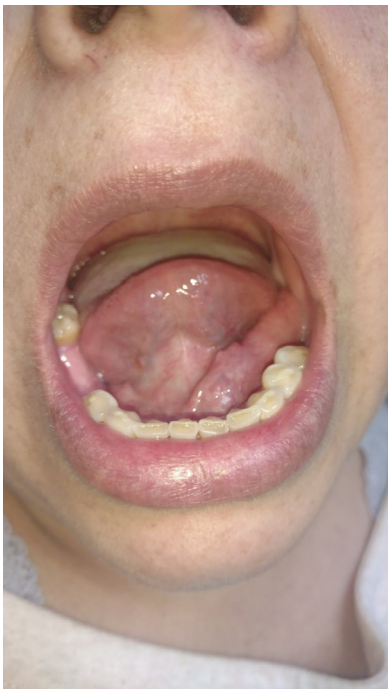

Fig. 1. Intraoral photo demonstrating left-sided floor of mouth elevation.

enhancement and coarse central calcification. The submandibular glands appear within normal limits" (Figures 2A, 2B). The patient was subsequently taken to the operating room for sublingual sialoadenectomy under general anesthesia. The specimen was submitted for histologic examination.

The surgical pathology slides were sent for consultation to the Oral and Maxillofacial Pathology Biopsy Service at Northwell Health/Long Island Jewish Medical Center. At lower power, the viable trabecular bone was appreciated in the center of the specimen, surrounded by hypercellular areas of mucocytes, intermediate cells, and epidermoid cells (Figures 3A, 3B). More traditional areas of multicystic mucoepidermoid carcinoma were appreciated at the periphery of the lesion (Figure 3C). Immunohistochemical stains for CK-7 and CK-19 were positive in the neoplastic cells. CK-20, CD-117, HBME-1, S-100, mammaglobin, DOG1, Bcl-2, and p-63 immunostains

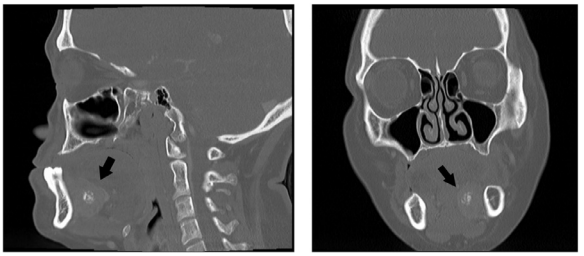

Fig. 2. **(A)** Sagittal and **(B)** coronal computed tomography imaging demonstrating floor of mouth mass and associated central calcifications.

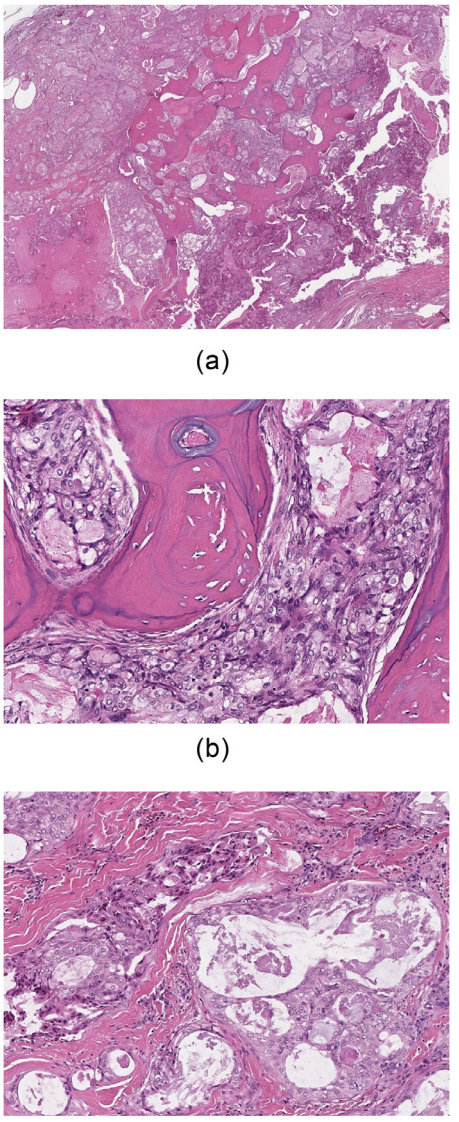

Fig. 3. **(A)** At low power, a central component of viable bone surrounded by cellular areas consisting of mucocytes, intermediate cells, and epidermoid cells is observed. **(B)** The mucoepidermoid carcinoma abuts the viable bone. **(C)** More traditional areas of multicystic mucoepidermoid carcinoma are appreciated at the periphery of the specimen. A high-resolution version of this slide for use with the virtual microscope is available as eSlide: VM06114.

were negative. The Ki-67 proliferative index was low. Periodic acid−Schiff stained the ducts and cyst-like space contents as well as the isolated clear and mucous cells. All periodic acid−Schiff positive cells were diastase resistant. Perineural invasion, necrosis, mitosis, and anaplasia/nuclear atypia were not identified; therefore, the mucoepidermoid carcinoma was classified as low-grade using AFIP criteria. A final diagnosis of low-grade

mucoepidermoid carcinoma with intratumoral bone formation was reported.

A 2-month follow-up CT scan of the head, neck, and chest did not show residual tumor in the operative bed or nodal involvement. Because of positive anterior and lateral microscopic margins, the patient was referred to our affiliated Head and Neck Surgical Service, where the patient underwent definitive treatment. After discussion at this institution's tumor board, treatment consisted of a wide local excision of the left floor of mouth with facial artery musculomucosal flap reconstruction. The final pathology demonstrated no signs of residual disease and no further therapy was recommended. There was no evidence of recurrence or metastasis 2 years after ablative surgery.

DISCUSSION

The first reported case of this malignancy dates back to 1921, though it was not termed mucoepidermoid carcinoma until analyzed by Stewart et al. in 1945.[1,22] It was not until 1984 when microscopic calcifications were identified as a novel finding in MEC.[1] Additional studies suggest that these calcifications may occur with more frequency than previously noted.[10]

Four mechanisms were proposed to explain calcifications within MEC: calcifications secondary to hypercalcemia, as a component of the tumor, as calcification of tumor necrosis, and as calcification of tumor secretions.[10,11,16] Histologically, these calcifications are identified as amorphous eosinophilic material forming irregular and concentric lamellar, Liesegang ring-like structures.[10,11] This structural pattern, along with recent immunohistochemical findings, suggests that dystrophic calcifications in mucoepidermoid carcinoma may be a result of mucin secretion by tumor cells.[11] This explanation would also support why the majority of these reported cases occur within MEC originating from the minor salivary glands.[10] Though originally thought to be associated with more aggressive disease, current evidence suggests that this finding is independent of MEC histologic grade and prognosis and are not considered as a part of AFIP or Brandwein grading criteria unless associated with frank tumor necrosis, which was not observed in our case.[8-10,15]

In 2015, MEC with intratumoral bone formation was first reported and remains, to our knowledge, the only previous case in the literature. The case exhibited notable clinical similarities to the case presented in this article.[15] The formation of osteoid in these 2 cases, as opposed to dystrophic calcifications described previously, suggests a different histopathologic mechanism.[15] A documented case of mature osteoid formation within a sialolith has been reported. Takeda et al. suggested that the progression from calcification, to immature woven bone, to mature bone after successive bony remodeling accounted for the presence of bone within their specimen.[17] This mechanism could account for the trabecular bone in our case, which may have resulted from calcifications arising from tumor secretions that evolved into mature, viable, trabecular bone.

Multiple studies have shown bone formation in pleomorphic adenoma (PA), a benign salivary gland tumor. First documented in 1954, Yates and Paget reported a PA containing bone formation within chondroid nodules, suggesting a mechanism of endochondral ossification.[18] Similar bony formation was noted by Lee et al. in a PA of the maxillary antrum.[19] Lacking any chondroid components, the authors suggested that the bone formation may be due to metaplasia of myoepithelial cells.[19] This mechanism was also suggested by Takeda and Yamamoto in their description of bone formation within a PA of the minor salivary glands.[20] Bone formation is considered exceedingly rare in salivary malignancies; however, a case of carcinoma ex-pleomorphic adenoma that exhibited trabecular bone formation has been documented.[21] In the 2 cases of bone formation in MEC (including this report), chondroid tissue has not been a documented finding, suggesting a metaplastic mechanism. Interestingly, Maruse et al. did note dystrophic calcifications adjacent to osteoid tissue and proposed that this may have acted as a substrate for bone formation.[15]

Though the mechanism of these unique findings remains unclear, the diagnosis and subsequent treatment of this disease is paramount. Clinically, these 2 cases of "ossifying" MEC presented as relatively painless swellings of the floor of the mouth. Routine radiography may show calcifications and bone formation as seemingly benign radiopacities, if visible at all. Taken together, these signs are often attributed to inflammatory diseases or benign lesions such as sialadenitis, sialolithiasis, and PA, which may delay proper diagnosis and treatment. The present case is meant to educate practitioners to be suspicious of these irregular findings and make sure a definitive diagnosis is reached in a timely fashion.

CONCLUSION

To our knowledge, this report describes the second case of trabecular bone formation observed within an MEC. This finding, though very uncommon, should be considered in forming a differential diagnosis. Thus, it is imperative that surgeons and pathologists are aware of this rare variant and consider it in the differential diagnosis when ossification is observed clinically, radiographically, grossly, and, especially, histologically.

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